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### MS-SMART study

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We thank Grech and colleagues for their letter concerning the recently published MS-SMART trial. This multi-arm phase 2b trial effectively condensed, into one well powered trial, the study of three repurposed drugs with distinct mechanisms of action potentially relevant to slowing progression in secondary progressive MS (SPMS). Despite positive experimental and early clinical work, sadly none had any effect on slowing the rate of whole brain atrophy (primary outcome), nor on a variety of secondary outcome measures.

One of our eligibility criteria was a Beck Depression Inventory II score that excluded patients with moderate-severe depression. Our rationale was that some of this group were likely to require a selective serotonin reuptake inhibitor (SSRI) during the 96 weeks of trial duration, and since it was fully blinded, they would have carried a 25% risk of being double-dosed. If an SSRI was felt to be indicated by treating neurologists, participants would therefore have needed to stop Investigational Medicinal Product (IMP), raising challenging ethical and practical issues for both participants and trial viability. Foremost in our consideration was recognition of the substantial investment that neuroprotective trial participants have in continuing to take IMP given their lack of existing therapeutic options. In effect, they would have been placed in the difficult position of having to choose between recommended treatment for their depression or hope in altering their disease trajectory through continued IMP dosing. Potential effects on trial viability would also have been substantial, with reduced dosing across all arms. Notwithstanding these difficult issues for trial design, the actual number who failed this screening criterion from the ineligible group were low, 7/90 (8%).

Grech and colleagues separately raise wider questions of the potential role for SSRIs in SPMS. While we were specifically concerned with testing neuroprotective agents that targeted abnormal axonal pathobiology, we agree that there are other potentially relevant mechanisms of action in this clinical context. First, the well-established efficacy of SSRIs in treating mood disorder (symptomatic treatment) that may consequently enable people with SPMS to better engage in rehabilitative or neurorestorative programmes. Secondly, a point that we cautiously discussed, is whether fluoxetine has any degree of 'anti-inflammatory' effect as shown by the reduction in new/enlarging T2 lesions (adjusted mean difference versus placebo 0.5 [95% CI 0.3-0.9;  $p=0.012$ ], table 3). This might be of interest, but of course would need to be pursued again in an inflammatory MRI paradigm applied to an appropriately selected trial population with relevant outcomes.

Our view is that there is no evidence in the broad progressing (as determined by clinical/MRI markers) SPMS phenotype enrolled in this study that fluoxetine has any neuroprotective effect: 96 week adjusted mean difference percentage brain volume change versus placebo - 0.1% [95% CI -0.5 to 0.3;  $p=0.86$ ], table 2. This also concurs with the independently reported FLUOX-PMS study. However we would not wish to dissuade investigators from considering evaluation of SSRIs in the group with moderate-severe depression.

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Basil Sharrack MD (12), Professor Christopher J Weir PhD (3), Professor Siddharthan Chandran PhD (2), on behalf of the MS-SMART Investigators.

**No change in COIs**